IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jens PETERSEN
Title:	**POLYACRYLAMIDE HYDROGEL FOR THE TREATMENT OF INCONTINENCE AND VESICOURETAL REFLUX**
Appl. No.:	09/938,667
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Examiner:	Blessing M. Fubara
Art Unit:	1618
Confirmation No.	2505

DECLARATION OF ROGER R. DMOCHOWSKI

UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Roger R. Dmochowski, hereby declare as follows:

(1) I am employed currently as a Professor in the Department of Urology at Vanderbilt University in Nashville, Tennessee. I also am Director of the Vanderbilt Continence Center at Vanderbilt University. I hold the degree of Doctor of Medicine and I am board-certified in the specialty of urology. My qualifications as an expert in the field of urology are detailed in an appended curriculum vitae (APPENDIX 1).

(2) I am a paid consultant to the assignee of this application, Contura International A/S, to which I provide clinical expert advice on designing and conducting clinical trials for BULKAMID, a prospective Contura product for urinary incontinence. I also serve as the Medical Monitor for an ongoing U.S. clinical trial of BULKAMID, in which capacity I review safety data. My compensation for these services is by arrangement involving no contingency related either to the application or to the performance or commercial success of BULKAMID. Accordingly, I have no personal interest in the disposition of the

application by the U.S. Patent and Trademark Office (PTO) or in the commercial status of BULKAMID.

(3) In relation to the application, the PTO has taken the position, I understand, that, in view of documented usage of acrylamide hydrogel to treat vesicoureteric reflux (VUR), a person knowledgeable in urology would have been motivated, *circa* August of 2000 (the "critical date"), to inject acrylamide hydrogel into the ostium of the urethra with the expectation that the hydrogel would increase resistance to the flow of urine in the urethra, thereby treating urinary incontinence (UI) in the manner of a bulking agent. Thus, I understand the PTO's position to be that the documented usage of a bulking agent, such as polyacrylamide hydrogel, to treat VUR would have suggested, as the critical date, using such bulking agent to treat UI.

(4) For the reasons elaborated below, however, I believe that those familiar with the two conditions, VUR and UI, would not have made this generalization, *a priori*, in view of the differences between (A) the active function of the ureter near the ureterovesical junction (UVJ), where introduction of bulking agent can ameliorate VUR, and (B) the function of the urethra at the level of the internal sphincter, where multiple factors affecting UI are not predictably addressed by simply introducing a bulking agent.

(5) The ureter is a muscular tube through which urine passes from the kidneys to the bladder, at the point of the ureteral opening. See appended FIGURE 1. The UVJ is formed by investment of the muscular walls of the ureter into the wall of the bladder, as FIGURE 2 shows in the schematic cross-section.

(6) Under normal conditions, when a bolus of urine is propulsed through muscular contraction distally at the level of the UVJ, the pressure of this bolus must exceed the passive pressure of the intravesical lumen for urine to pass through the UVJ and into the bladder. Under normal circumstances, the contraction wave of the muscular contraction of the ureter is able to propulse the urine bolus distally. This pressure exceeds the pressure in bladder and forces the urine through the UVJ. There is a small contracted ureteral ring just proximal to the ureteral orifice at the UVJ, which helps with anti-reflux, *i.e.,* with prevention of urine from going in the opposite direction up to the kidney, at this

level. As the urine bolus enters the bladder, the ureter retracts again within its sheath, telescoping the ureter and, hence, decreasing resistance to flow and facilitating urine passage into the bladder. This is an active mechanism, essentially a conduction of muscular contraction through the walls of the UVJ, propulsing a bolus of urine through this area.

(7) If there is an inability of a contraction wave to occlude the ureter completely, then urine may flow in the opposite direction from normal, a phenomenon that characterizes VUR. This also occurs in situations where the UVJ is pathologically wide or weakly contracting. In each instance, there is a failure at this level to propagate the above-mentioned muscular contraction.

(8) Introduction of a bulking agent into the ureter at the UVJ was an approach, known at the critical date, for treating VUR by increasing pressure on the ureter, thereby eliminating the reverse urine flow that characterizes VUR. In other words, this approach remediates a single physical dysfunction, failure of muscular contraction at the UVJ, by means of a physical support for the ureter at that level.

(9) In the UI context, by contrast, the function of the internal sphincter of the urethra, the muscle that constricts the internal urethral orifice (see FIGURE 1), is for tonic closure, thought to be mediated both by neural and muscular conditions. Under no circumstances is a wave of muscular contraction propagated to the urethra from the bladder. Rather, the function of the urethra is to form a bolster or closure mechanism, much like a washer in a faucet, for purposes of prevention of urine flow through the lumen of the urethra.

(10) Under normal circumstances in a continent patient, urination begins via short-segment neural activity, which causes the smooth muscle of the sphincter to relax and urine to be propagated through the lumen by the pressure generated by more proximal bladder contraction. In a patient who suffers from UI, the overall closure generated by the coaptation of the muscle is less, due to intrinsic muscular damage, intrinsic neural damage, or a combination of both, such that the closure mechanism of the urethra is weaker and passive loss of urine can occur due to gravitational and/or effort-related events.

(11) Unlike the situation of the ureter in VUR, therefore, the closure mechanism of the urethra is not purely muscular. Rather, the overall closure mechanism also involves a rich vasculature or blood vessel-vein plexus, as well as the actual mucosa or epithelial lining of the urethra. [Wein, 1992; deGroat et al, 1993; Sugaya et al, 1997; Yoshimura and deGroat, 1997] Thus, all three factors can be involved in the urethral closure mechanism, in sharp contrast to the ureter, which is purely a muscular structure and dependent on the propulsion of boluses of urine propagating through the area of the UVJ.

(12) Dysfunction in the urethral closure mechanism, manifested as UI, likewise is effected by an interaction of three factors mentioned above. The resultant complexity of UI etiology undercuts any reasonable expectation, *a priori*, that UI could be treated by means of a simple physical expediency, namely, introducing bulking agent into the urethra. [In fact , prior to the initial use of Teflon, bulking of the urethral function and the fact that simple passive resistance represents only one component of urethral function, bulking was not considered a reasonable option for loss of urethral functional integrity. Certainly obstruction of the urethra could be obtained with any material, however the dual qualities of passive resistance during filling without active obstruction during voiding seemed to be unattainable with materials science of that time. The expanded use of bovine collagen in the mid to late nineteen nineties was the first generalized use of a material for this purpose with proven success.]

(13) For the reasons stated above, I conclude that a person with a background in urology would have understood, at the critical date, that the active function of the ureter near the UVJ differs fundamentally from the function of the urethra at the level of the internal sphincter, and that this difference underscores a corresponding delineation between the dysfunctions responsible for VUR and UI, respectively. By virtue of this delineation, moreover, I believe that such a person would not have generalized from (i) documented usage of a bulking agent for treating VUR to (ii) a suggestion of using such bulking agent to treat UI.

(14) I further declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so

made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 7/30/08

By: _____
Roger R. Dmochowski, M.D.

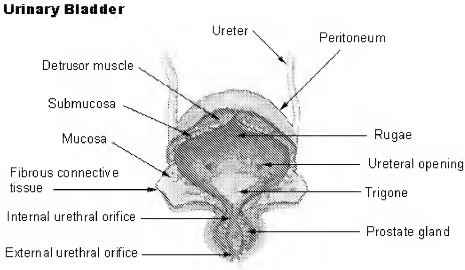
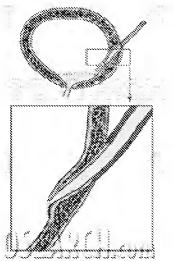


Figure 1



Ureterovesical Junction

Figure 2

Wein AJ: *Neuromuscular dysfunction of the lower urinary tract*. In: Walsh PC, Retik AB, Stamey TA, Vaughan ED, ed. *Campbell'sUrology*, 6th ed.. Philadelphia: WB Saunders; 1992:573-642.

de Groat WC, Booth AM, Yoshimura N: *Neurophysiology of micturition and its modification in animal models of human disease*. In: Maggi CA, ed. *The Autonomic Nervous System, vol 3, Nervous Control of the Urogenital System*, London: Harwood Academic; 1993:227-290.

Sugaya K, Roppolo JR, Yoshimura N, et al: The central neural pathways involved in micturition in the neonatal rat as revealed by the injection of pseudorabies virus into the bladder. *Neurosci Lett* 1997; 223:197.

Yoshimura N, de Groat WC: Neural control of the lower urinary tract. *Int J Urol* 1997; 4:111.